butylmagnesium chloride with boron fluoride produces *t*-butyldiisobutylborane,[3] obviously with rearrangement of two alkyl groups, the corresponding reaction of the neopentyl Grignard reagent was considered worthy of study. Interest was stimulated also by the fact that all attempts to prepare sterically crowded tri-*t*-butylborane in this laboratory have failed, regardless of the method tried.[4]

In the early stages of this investigation many attempts to prepare neopentylmagnesium chloride by the ordinary method[5] surprisingly failed, both in ether and in tetrahydrofuran. The apparent reaction of the chloride with magnesium turnings could be sustained only as long as an active halide, such as methyl iodide or ethyl bromide, was added also. Recourse was therefore made to the massive entrainment method of Pearson,[6] using 1 equiv of ethylene dibromide with ether as the solvent and this technique was successful in every experiment.

The reaction of the Grignard reagent with boron fluoride etherate then consistently gave trineopentylborane in 50–60% yields. The structure of this compound was proved by the facts (a) that oxidation with alkaline hydrogen peroxide gave neopentyl alcohol (no other alcohols) identified by glpc, and (b) that the pmr spectrum had two singlets, one at 1.04 and the other at 1.46 ppm below TMS. Based on the relative areas of 4.5 to 1, the 1.04 peak is assigned to the methyl protons and the 1.46 peak to the methylene protons.

Trineopentylborane proved to be stable to distillation, even at atmospheric pressure [bp 227° (747 mm)]; distillates showed no evidence of decomposition or isomerization. Unlike other primary trialkylboranes, it does not react with boron chloride[7] up to 175° (no RBCl$_2$ or R$_2$BCl detected). The failure of this reaction suggests that BH species may be required for the process as suggested by Koster's observation[8] that diborane acts as a catalyst for the reaction of boron chloride with trialkylboranes.

Studies of the behavior of trineopentylborane when heated with other trialkylboranes (alkyl group redistribution reactions) will be reported in a later paper.

Experimental Section

Neopentyl chloride, purchased from K & K Laboratories, Plainview, N. Y., was distilled through a spinning-band column: bp 83.0–83.2°; n^{25}D 1.4041; d^{25} 0.8654; glpc pure. Ethylene dibromide was dried over calcium chloride and distilled before use.

Neopentyl Grignard Reagent.—A mixture of 51 g (2.1 g-atoms) of magnesium turnings, 500 ml of anhydrous ether, and 106 g (1 mole) of neopentyl chloride was stirred under dry nitrogen and a solution of 186 g (1 mole) of ethylene dibromide in 500 ml of ether was then added dropwise over a period of 17 hr. The entire mixture was then boiled with stirring for an additional 3

hr. Additional ether (total 500 ml) was added periodically to maintain fluidity.

Trineopentylborane.—Boron fluoride etherate (46 g, 0.32 mole) was added dropwise to the Grignard reagent with stirring under dry nitrogen (exothermic reaction). The reaction mixture was stirred for an additional 2 hr and cooled, and 620 ml of cold water was added. The upper ethereal layer was removed by siphoning under nitrogen pressure and the lower layer was washed twice with ether in the same manner. The combined ethereal solution was dried over calcium chloride and distilled. The fraction with bp 50–52.6° (0.5–0.6 mm) was retained (55% yield). Redistillation gave pure product: bp 67.5° (1.4 mm), 164° at (143 mm), 227° (747 mm); n^{25}D 1.4356; d^{25} 0.7634.

Anal. Calcd for C$_{15}$H$_{33}$B: B, 4.83; MR$_D$, 76.5. Found: B, 4.82, 4.83; MR$_D$, 76.6.

Registry No.—[(CH$_3$)$_3$CCH$_2$]$_3$B, 7687-73-2.

The Course of the Mannich Reaction with Methyl Isobutyl Ketone. Preparation of 2-Isopropyl-1-butenone-3

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Having need of 2-isopropyl-1-butenone-3 (1) for use in synthesis, we ran the Mannich condensation of methyl isobutyl ketone (2) with formaldehyde and diethylamine hydrochloride, a reaction which is reported[2] to afford 3-(N,N-diethylaminomethyl)-4-methylpentanone-2 (3), a precursor or functional equivalent of 1. This Mannich reaction has, in fact, recently been described[3] as a high-yield (94.5%), commercial-scale source of 1.

When this reaction was run in our laboratory, however, there was obtained in 63% yield a product, bp 70–82° (3.5 mm), whose nmr spectrum displayed *no* acetyl methyl singlet. This material was converted to its hydrochloride (89%) and distilled to afford a vinyl ketone (34%) whose nmr spectrum also showed no acetyl methyl singlet and had a vinyl proton region essentially identical with that of methyl vinyl ketone. These properties clearly indicated that this Mannich product contained virtually no 3, but was instead Mannich base 4, resulting from condensation at the methyl group of 2. The identity of the vinyl ketone obtained was confirmed as 5-methyl-1-hexenone-3 (5), a readily polymerized substance which formed a 2,4-dinitrophenylhydrazone with mp 104–106.5°. Several repetitions of the procedure afforded identical results; no nmr acetyl methyl singlet ascribable to 3 was detected.[4]

The Mannich reaction of 2 was also run with dimethylamine hydrochloride and the same nmr results

(3) (a) G. F. Hennion, P. A. McCusker, and A. J. Rutkowski, *J. Am. Chem. Soc.*, **80**, 617 (1958); (b) G. F. Hennion, P. A. McCusker, and J. V. Marra, *ibid.*, **81**, 1768 (1959).

(4) Despite many literature references to tri-*t*-butylborane, this compound remains unknown to this date. Our studies lead to the conclusion that workers who alleged making or using this compound actually had either tri-isobutyl- or *t*-butyldiisobutylborane.[3b]

(5) F. C. Whitmore, *et al.*, *J. Am. Chem. Soc.*, **61**, 1585 (1939); **64**, 1239 (1942).

(6) D. E. Pearson, D. Cowan, and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).

(7) P. A. McCusker, G. F. Hennion, and E. C. Ashby, *J. Am. Chem. Soc.*, **79**, 5192 (1957).

(8) R. Koster, *Angew. Chem.*, **73**, 66 (1961).

(1) (a) Alfred P. Sloan Foundation Research Fellow. (b) Recipient of support under the terms of an institutional research training grant from the U. S. Public Health Service, summer 1966.

(2) R. Heilmann, G. de Gaudemaris, and P. Arnaud, *Compt. Rend.*, **234**, 1177 (1952).

(3) M. I. Farberov and G. S. Mironov, *Dokl. Akad. Nauk SSSR*, **148**, 1095 (1963); *cf. Chem. Abstr.*, **59**, 5062 (1963).

(4) Possibly the composition of the products obtained by previous investigators differed from that reported here. However, insufficient information is given in either ref 2 or 3 to come to any conclusion about this possibility, and no reasons are given in these articles for the structural assignments made.

were obtained.[5] In this case pure 5 was obtained in 18% yield from Mannich base 6 by preparation and decomposition of its hydrochloride.

The base-catalyzed aldol· condensation of 2 with formaldehyde has also been reported[6] to yield 1, after iodine-catalyzed dehydration of initially isolated ketol 7. Repetition of these procedures afforded an α,β-unsaturated ketone with an nmr spectrum (see the Experimental Section) which unequivocally confirmed its identity as desired 1. Compound 1 formed a 2,4-dinitrophenylhydrazone with mp 112.5–114°. The nmr spectrum of crude unsaturated ketone from this aldol route showed the presence of a small amount of 5.

Synthesis of 1 was also carried out by the following unambiguous route. Ethyl isopropylacetoacetate (8) was converted to ketal 9, which, after reduction with lithium aluminum hydride and acidic work-up, afforded 7, the ketol precursor of 1.
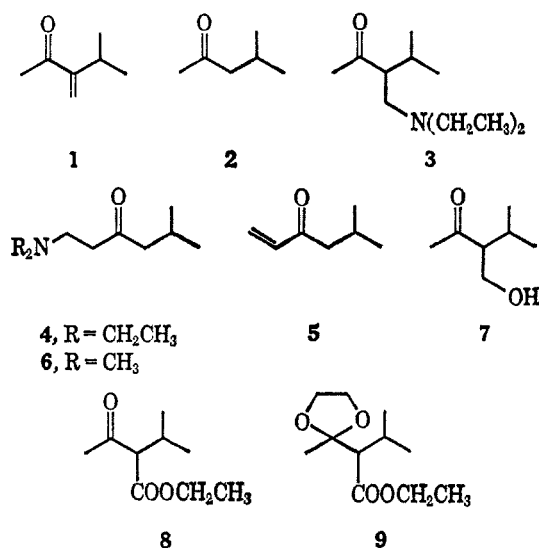
The Mannich reaction of unsymmetrical ketones has provided other examples of disagreement in the literature over the course of the reaction.[7] Buchanan has very recently uncovered the source of much of this disagreement by demonstrating that the structure of Mannich bases often cannot be inferred from the structures of products obtained from their reactions, since rearrangement of the Mannich base may occur.[8]

The question remains, however, of what are the controlling factors in the course of the original formation of the Mannich base. After reinvestigation of the Mannich reactions of 2-methylcyclopentanone and 2-methylcyclohexanone,[9] House conjectured that "under the usual slightly acidic reaction conditions" of the Mannich reaction "unsymmetrical ketones will react predominantly at the more highly substituted α

position, corresponding to the more stable enol."[10] Certainly methyl isobutyl ketone (2) does not afford the product of reaction at the more highly substituted position. Data of House and Kramar[11] on the equilibrium composition of enol acetates derived from 2 (95% 10 vs. 5% 11) suggest that isolation of 4 does not correspond to product formation at the site of the more stable enol.[12] Available data on rates of acid-catalyzed enolization,[13] on stability and reactivity of isomeric enols, and on reversibility of condensation reactions do not permit any conclusion about what the controlling factors are. Until a careful study of reaction variables has been made, caution in predicting the orientation of the Mannich and related condensations with unsymmetrical ketones appears advisable.

10   11
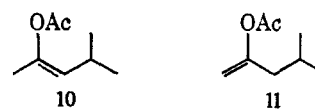
Experimental Section[14]

Mannich Reaction of Methyl Isobutyl Ketone (2). A. Using Diethylamine Hydrochloride.—No procedural details are given in the reported[2] preparation of 3. The procedure described here is based on that of Wilds, et al., for the preparation of 1-diethylamino-3-butanone.[15] A mixture of 75.0 g (0.75 mole) of methyl isobutyl ketone, 6.60 g (0.22 mole) of paraformaldehyde, 16.3 g (0.163 mole) of diethylamine hydrochloride, 7 ml of methanol, and 8 drops of concentrated hydrochloric acid was refluxed for 6 hr. To the cooled mixture was added a solution of 6 g of sodium hydroxide in 28 ml of water. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated to leave a residue which was distilled to give 18.92 g (63%) of pale yellow Mannich base 4: bp 70–82° (3.5 mm); $n^{25}D$ 1.4351 [lit.[2] bp 73° (2 mm); $n^{18}D$ 1.4410]; λ_{max} 5.82 μ; $\delta_{TMS}^{CCl_4}$ 0.84–1.08 [12 H, superimposed d, $(H_3C)_2CH$ and t, 2 H_3CCH_2N] and ca. 1.85–2.85 ppm (11 H, including q, 2 H_3CCH_2N). There was no significant absorption in the nmr spectrum between 2.00 and 2.15 ppm. 3,3-Dimethyl-4-(N,N-dimethylamino)butanone-2, a close analog of 3, displays a 3 H singlet at 2.07 ppm in deuteriochloroform.[7b] Accordingly, no more than at most a trace of 3 (or 2) was present in our product.

Hydrogen chloride was bubbled through a solution of 17.90 g (0.097 mole) of 4 in 500 ml of ether for 30 min. The precipitate of hydrochloride was collected and weighed, after drying, 19.16 g (89%): $\delta_{TMS}^{CDCl_3-CCl_4}$ 0.92 [6 H, d, J = 7 cps, $(H_3C)_2CH$], 1.38 (6 H, t, J = 7 cps, 2 H_3CCH_2N), and multiplets from ca. 1.8 to 3.3 ppm including the quartet for 2 H_3CCH_2N centered at ca. 3.08 ppm. Again, there was no significant absorption which could be ascribed to a 3 H singlet in the 2.0–2.2-ppm region.

Distillation of 12.07 g (0.065 mole) of the hydrochloride at reduced pressure in the presence of 0.5 g of hydroquinone[7b] afforded 2.10 g (34%) of essentially pure 5, bp 56–58° (ca. 60

1   2   3

4, R = CH₂CH₃
6, R = CH₃

5   7

8   9

(5) (a) G. L. Buchanan and A. C. W. Curran (private communication from Dr. Buchanan) have also found that the product from the Mannich reaction of 2 with dimethylamine hydrochloride is 6, on the basis of its nmr spectrum. This finding agrees with an earlier assignment of structure: (b) R. Jacquier, M. Mousseron, and S. Boyer, *Bull. Soc. Chim. France*, **23**, 1653 (1956).

(6) J. Colonge and L. Cumet, *ibid.*, **14**, 838 (1947).

(7) For example, in the case of methyl isopropyl ketone, *cf.* (a) ref 5b; (b) M. Brown and W. S. Johnson, *J. Org. Chem.*, **27**, 4706 (1962); (c) N. B. Haynes and C. J. Timmons, *J. Chem. Soc., Org. Sect.*, 224 (1966). The findings of Haynes and Timmons have been confirmed by G. L. Buchanan and A. C. W. Curran (private communication).

(8) G. L. Buchanan and A. C. W. Curran, *Chem. Commun.*, 773 (1966).

(9) H. O. House and B. M. Trost, *J. Org. Chem.*, **29**, 1339 (1964).

(10) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 231.

(11) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

(12) For an earlier study of enol acetylation of 2, see E. H. Man, F. C. Frostick, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **74**, 3228 (1952). Using an indirect determination of isomer distribution which did not identify a majority of the product, these workers found at 100° a 28:72 ratio of 10:11 and at room temperature of an 82:18 ratio of 10:11.

(13) H. M. E. Cardwell and A. E. H. Kilner [*J. Chem. Soc.*, 2430 (1951)] report a slightly greater rate of enolization of 2 toward the methylene group on the basis of analysis of the composition of bromination products.

(14) Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points and boiling points are not corrected. Ultraviolet spectra were determined on a Bausch & Lomb Spectronic 505 spectrometer and infrared spectra were determined on a Perkin-Elmer Model 21 spectrometer. Vpc was done on a Wilkens Aerograph A-700 instrument. Nmr spectra were run on a Varian Model DA-60-I instrument.

(15) A. L. Wilds, R. M. Nowak, and K. E. McCaleb, *Org. Syn.*, **37**, 18 (1957).

mm).[16] Vpc analysis on a 9-ft 7.5% Carbowax column a 125° and on a 20-ft silicone SE-30 column at 125° showed only one major peak, which, when collected, had λ_{max} 5.93 (shoulder at 5.86) and 6.18 μ; $\lambda_{max}^{95\% \text{ EtOH}}$ 212 mμ; $\delta_{TMS}^{CCl_4}$ 0.93 [6 H, d, J = 6 cps, $(H_3C)_2CH$], 1.9–2.5 (3 H, broad multiplet), 5.61, 5.67, 5.74, 5.80, 6.15, 6.22, and 6.29 ppm [prominent peaks of an ABX pattern for the three vinyl protons very similar to that (5.76, 5.82, 5.89, 5.96, 6.20, 6.27, and 6.34 ppm) of methyl vinyl ketone].

Pure 5 tended to polymerize rapidly;[16] it afforded a 2,4-dinitrophenylhydrazone, mp 104–106.5°.

Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52. Found: C, 53.32; H, 5.64.

Crude Mannich base 4 afforded a 2,4-dinitrophenylhydrazone, mp 169–172°. The melting point reported[2] for the 2,4-dinitrophenylhydrazone of the claimed compound 1 prepared *via* this Mannich procedure was 171°. No attempt was made in the present investigation to determine the structure of the 169–172° material.

B. Using Dimethylamine Hydrochloride.—The same procedure described above was followed, using 12.1 g (0.147 mole) of dimethylamine hydrochloride. Distillation of the crude product afforded one main fraction of 12.96 g (56%) of 6: bp 59–60° (1.25 mm); λ_{max} 5.83 μ; δ_{TMS} 0.90 [6 H, d, J = 6.5 cps, $(H_3C)_2$-CH], and 2.14 ppm [s, $(H_3C)_2N$, accurate integration impossible owing to underlying methylene resonances].

Ethyl 2-Isopropyl-3-ethylenedioxybutyrate (9).—According to a procedure of Corey and Gregoriov,[17] a mixture of *ca.* 0.2 g of *p*-toluenesulfonic acid monohydrate, 5.0 ml of ethylene glycol, bp 63–66° (0.2 mm), and 5.01 g (0.0250 mole) of ethyl isopropyl-acetoacetate (8)[18] in 300 ml of dried benzene was refluxed for 48 hr attached to a water separator, cooled, and partitioned between 5% sodium bicarbonate solution and ether. The ether-benzene layer was washed with water and dried over magnesium sulfate. Evaporation of the solvents afforded 6.33 g of slightly yellow oil (theoretical yield of 9: 6.28 g). Vpc analysis of this material on a 20% Carbowax column at 135° showed only one major component plus a very small amount of what was probably ethylene glycol (by retention time). The purified ketal 9 collected by vpc had λ_{max} 5.75 μ; $\delta_{TMS}^{CCl_4}$ 0.84 and 0.97 (2 d, each 3 H with J = 6 cps, H_3CCCH_3), 1.21 (3 H, t, CH_3CH_2), 1.36
H
(3 H, s, CH_3COO), *ca.* 2.1 [1 H, broad m, $HC(CH_3)_2$], 3.86 (4 H, bunched multiplet, OCH_2CH_2O), and 4.04 ppm (2 H, q, OCH_2CH_3).

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.92; H, 9.31.

2-Isopropyl-1-butenone-3 (1). A. *Via* Reduction of Ketal 9 with Lithium Aluminum Hydride.—The 6.33 g of crude 9 prepared above was dissolved in 50 ml of anhydrous ether and the resulting solution was added dropwise to a stirred mixture of 2.07 g (0.0546 mole) of lithium aluminum hydride and 100 ml of anhydrous ether. After the addition was completed, the solution was allowed to stand at room temperature for 15 min, and then was refluxed for 30 min. Cold water (10 ml) was added cautiously, followed by 100 ml of 25% sulfuric acid, and the mixture was stirred for 15 min. The aqueous layer was separated and extracted with three 100-ml portions of ether. The combined ether layers were washed with water and saturated sodium bicarbonate solution, and dried over magnesium sulfate. Evaporation of the ether afforded 2.43 g (73% from 8) of crude 7: λ_{max} 2.90 and 5.82 μ; $\delta_{TMS}^{CCl_4}$ 0.92 [6 H, d, $(H_3C)_2CH$], 2.13 (3 H, s, H_3CC), and 3.94 ppm (1 H, s, OH). Attempts to purify 7 by vpc were unsuccessful since it decomposed to 1 on the column.

The procedure of Colonge and Cumet[6] for preparing 1 from 7 by distillation from iodine was used. The reported yield of 63% was not achieved in our hands, although extensive efforts to maximize yield were not made. From a 2.30-g (0.0177 mole) sample of crude 7 prepared from 9 there was obtained, after careful refractionation to remove the eliminated water and other

impurities, only 0.39 g (20%) of 1: bp 132–133° (lit.[5] bp 134–136°); λ_{max} 5.95 and 6.13 (w) μ; $\lambda_{max}^{95\% \text{ EtOH}}$ 221 mμ (ϵ 9200); $\delta_{TMS}^{CCl_4}$ 1.00 [6 H, d, J = 6 cps, $(H_3C)_2CH$], 2.26 [3 H, s, $H_3CC(=O)$], 2.98 [1 H, m, $HC(CH_3)_2$], 5.63 (1 H, d, J = 1 cps), and 5.90 ppm (1 H, s, $\overset{H}{\underset{H}{>}}C=C<$).

Analytically pure 1 was prepared by vpc on a 20% Carbowax column at 110°.

Anal. Calcd for $C_7H_{10}O$: C, 74.95; H, 10.78. Found: C, 74.73; H, 10.79.

The 2,4-dinitrophenylhydrazone derivative prepared from 1 by the usual procedure had mp 112.5–114°.

A very small amount of another substance appeared on vpc analysis of the distilled 1. Its infrared spectrum (no OH or C=O stretch bands) and nmr spectrum $\{\delta_{TMS}^{CCl_4}$ 1.05 [6 H, d, J = 7 cps, $(H_3C)_2CH$], 1.39 (3 H, s, $H_3CC<\overset{O}{\underset{O}{}}$), 3.76 (4 H, bunched multiplet, OCH_2CH_2O), and 4.83 (1 H, m), and 5.16 ppm (1 H, d, J = 1 cps, $\overset{H}{\underset{H}{>}}C=C<$)] suggested that it was 2-isopropyl-3-ethylene–dioxybutene-1.

B. *Via* Aldol Condensation of Methyl Isobutyl Ketone with Formaldehyde.—According to the procedure of Colonge and Cumet,[6] a mixture of 250 ml of methyl isobutyl ketone, 62 ml of 40% aqueous formaldehyde, 1 g of sodium hydroxide, and 100 ml of 95% ethanol was allowed to stir at room temperature for 3 hr. The mixture was acidified to pH 6 with concentrated hydrochloric acid and reduced in volume to *ca.* 100 ml by distillation at aspirator pressure. The residue was filtered from precipitated salt and distilled to afford 20.73 g of crude 7: bp 82–90° (8 mm); λ_{max} 2.88 and 5.83 μ; $\delta_{TMS}^{CCl_4}$ 0.92 [d, J = 6 cps, $(H_3C)_2CH$] and 2.14 [s, $H_3CC(=O)$] ppm. Vpc analysis of this product showed three major and four minor components; no attempt was made to separate and identify these.

Distillation of this product from iodine (as described above) and redistillation afforded 7.64 g of 1 contaminated with a small amount of 5 (detected in the nmr vinyl proton region). In another preparation the only contaminant in the 1 was a small amount of 2. Thus, usefully pure 1 can be prepared conveniently by the base-catalyzed aldol condensation route.

A Convenient Synthesis of
2-Methylcyclopentane-1,3-dione

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Previously[1] a number of methods have been described for the preparation of 2-methylcyclopentane-1,3-dione (II), a key intermediate for the total synthesis of steroids.[2] These syntheses suffer from their multiplicity of steps and/or their low over-all yields.

(16) Preparation of **5**, bp 62° (52 mm), by the reaction of isoamoyl chloride with ethylene and aluminum chloride has been reported by P. R. Thomas, C. J. Tyler, T. E. Edwards, A. T. Radcliffe, and R. C. P. Cubbon, *Polymer*, **5**, 525 (1964). The product, which polymerized readily, was characterized by reduction to the saturated ketone and preparation of the semicarbazone of the latter.

(17) E. J. Corey and G. A. Gregoriov, *J. Am. Chem. Soc.*, **81**, 3124 (1959).

(18) W. B. Renfrow, Jr., *ibid.*, **66**, 144 (1944).

(1) H. Orchin and L. W. Butz, *J. Am. Chem. Soc.*, **65**, 2296 (1943); J. J. Panouse and C. Sannié, *Bull. Soc. Chim. France*, 1036 (1955); C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 2022 (1959).

(2) T. B. Windholz and M. Windholz, *Angew. Chem., Intern. Ed. Engl.*, **3**, 353 (1964).